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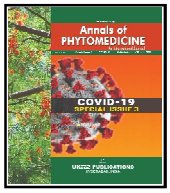

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Antiviral potential of frequently used plants in herbal formulations as immunity enhancers against SARS-CoV-2

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Abstract

A severe acute respiratory syndrome (SARS) is an extraordinary type of communicable infection that is caused by SARS-coronavirus. Since last two years, the entire world is fighting with this highly infectious disease and researchers are devoting all their labours to develop vaccines and few vaccines with remarkable efficacies have been developed. However, the great rate of mutations in SARS-CoV-2 annoying everyone. Though, the scientific communities are doing their best towards neutralizing the impact of infection yet the best way to combat this virus and future similar infections is to boost our immune system in a natural way. In this review, the prospective of widespread and easily available plants have been discussed as immunity enhancers to combat COVID-19 and other viruses.

1. Introduction

At the end of the year 2019, the citizens of the Hubei state (Wuhan city) of China were infected from lethal "SARS-CoV-2" which was subsequently termed as COVID-19 by the World Health Organization (WHO) (Wang *et al*., 2020). From its onset, the expansion, lethality and mutations of COVID-19 are increasing continuously, though the present situation is improving yet a threat is always there. There have been millions of definite cases of COVID-19 were reported till date in most of the countries worldwide with alarming number of deaths (https://covid19.who.int/). At the outset, the WHO affirmed it a civic health crisis of global concern and later on designated as a pandemic with symptoms of elevated body temperature, sneezing, sore throat, dry cough, diarrhea, depression, respiratory suffering, and obstruction of inhalation. The SARS-CoV-2 is an associate of α-coronavirus and is established parallel to previously reported severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) considering its mode of infection, disease cycle and clinical scale (Gurunathan *et al*., 2020). Later, through detailed study, it was found that these viruses of family Coronaviridae consist of envelope, a non-segmented + strain RNA similar to other members of the family, but coronaviruses are highly pleomorphic with a diameter of 80-220 nm and their genome size ranges from 26-32 kbs (MacLachlan and Dubovi, 2017). This virus is also different from MERS-CoV in amino acid sequence, particularly in the region of 1ab polyprotein and S-protein (surface glycoprotein) (Kannan *et al*., 2020). The entire cycle of replication of these viruses occurs in the cytoplasm of the host cells and causes a range of ailments.

The coronavirus is capable to attack and infect all types of populace, particularly aged patients suffering with hypertension, diabetes, chronic bronchitis, cardiovascular disease, cerebral infarction, chronic obstructive pulmonary disease, Parkinson's disease and cancer (Guan *et al*., 2020; Deng and Peng, 2020; Huang *et al*., 2020). Coronaviruse (CoV) enters into the host cell during dealings between the viral 'S' protein and the host cell's receptor protein, then it will binds with the angiotensin-converting enzyme 2 receptor of the host cell to produce a apposite environment for viral replication (Walls *et al*., 2020).

The epidemic of SARS-CoV-2 led to shattering actions, as there was little specific treatment known for coronavirus. Though, many vaccines have been developed and vaccination programs are on full swing yet it is a known fact that boosting the immunity is the best approach to combat these types of epidemics. Consequently, there is a worldwide demand to look for those agents that can work against SARS-CoV-2 as a preventive measure by boosting the immunity of populace. In India, the Ministry of AYUSH has also released a recommendation to use Ayurveda for improving the immunity for self-care against COVID-19. The Ayurveda suggests to utilize certain spices, *viz*., coriander, turmeric, garlic, cumin, *etc*., in cooking (Alam, 2019). The ministry also advised to drink herbal tea or decoctions containing ginger, basil, black pepper, cinnamon and raisin on regular basis (https://www.ayush.gov.in/). Consequently, the focus of people around the world was shifted towards natural-derived compounds that were constantly become a valuable curative options against numerous diseases and effective against viral infectivity, because they are naturally better adapted to the human body with minimum side effects (Alam *et al*., 2019; Chandra *et al*., 2019).

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Taking into consideration, thousands of plants have been comprehensively evaluated worldwide owing to their elevated antioxidant content and antimicrobial activity and their advantageous possessions on human beings. Plants hold many bioactive phytoconstituents such as phenols, alkaloids, flavonoids, sulfur-containing compounds, tannins, *etc*. (Yashin *et al*., 2017). As a result, numerous plant species have been evaluated and some of them have been validated for their medicinal value for curing diverse diseases (Dev, 1997). This article provides the phytochemistry and antiviral activities of selected plants that can be evaluated further for their antiviral potential.

2. Antiviral properties of plants

Varieties of plants are identified as immunity boosters, namely; *Ocimum basilicum* (Tulsi), *Zingiber officinale* (Adrak), *Allium sativum* (Garlic), *Cinnamomum* spp. (Dal-cheeni), *Tinospora cordifolia* (Giloy), *etc*. These herbs and spices are also used to treat respiratory problems (Singh *et al*., 2016). Likewise, common kitchen's herbs and spices, *e.g*., turmeric, clove, ginger, cinnamon, black pepper, *etc*., are well known as immunity boosters that help to combat viral infections (Sharma *et al*., 2017; Srivastava *et al*., 2020). In this article, the antiviral potential of six commonly used plants in Ayurveda and Unani formulations, *viz*., *Cassia fistula*, *Cinnamomum* spp., *Glycyrrhiza glabra* L., *Piper nigrum* L., *Syzygium aromaticum* L., and *Zingiber officinale* Roscoe have been discussed as they are frequently used to enhance immunity against SARS-CoV-2 during the pandemic. All these plants are already present in many herbal formulations against respiratory problems.

2.1 *Cassia fistula* L.

Cassia fistula L. (Fabaceae) is a commonly growing plant in tropics, subtropics and semi-arid regions of the world. This plant is extensively recognized for its medicinal properties as in ancient literatures related to medicinal plants. This plant is illustrated to be useful as herbal remedy against skin diseases, hepatic problems, tuberculosis, leucoderma, diabetes, rheumatism, *etc*. (Alam *et al*., 1990; Asolkar *et al*., 1992; Bhakta *et al*., 1999). Further, the anti-inflammatory, hypoglycemic and laxative activities have been reported (Kumar *et al*., 2006). The antifertility (Yadav and Jain, 1999), antioxidant, antitumor and antimicrobial properties of this plant were also reported (Panda *et al*., 2011). Usually, the leaves, tender shoots and flowers have been used to get the extract.

A range of anthraquinones have been isolated from *C. fistula* and subsequent characterization was done. The obtained results using mature leaves of the plant have validated that anthraquinone glycosides such as chrysophanol, rhein and physcion are there in good quantities. Beside leaves, the young green pods can also be used to extract the bioactive compounds (Dickert *et al*., 1981). Jangir and Jain (2018) investigated the antioxidant possessions of the fruit extract of *C. fistula* to ascertain its method of action. They showed that the hydroalcoholic take out of the fruit pulp demonstrated remarkable antioxidant properties.

The antiviral potential of *C. fistula* (fruits) was estimated in ethanol and it was reported that the extract was able to inhibit the foot and mouth disease (FMDV) causing virus. Likewise, pods and bark extracts in ethanol were reported toxic against the ranikhet disease virus (RDV) and Vaccinia virus (VV) (Sundararaju and Saritha, 2006). The extracts of leaf and young pods in hot water were estimated inhibitory against infectious boive rhinotracheitis (IBR) virus (Kainsa and. Kumar, 2012). Based on past experiments, it can be assumed that this plant has noteworthy antiviral potential and should be studied further in this regard as this plant is an important ingredient of 'coronil kit', a Patanjali product against coronavirus infection.

2.2 *Cinnamomum* spp.

Genus *Cinnamomum* is an aromatic tree which belongs to family Lauraceae. This plant is commonly known as 'Cinnamon' and has been significantly used in conventional Ayurveda and Unani medicinal systems. Cinnamon has been an admired spice in making food by several nations around the world since olden times. Cinnamon is acquired from the bark of juvenile branches to be used as an everyday condiment in kitchens. Beside this, the bark is used as a substance for herbal formulations of high therapeutic value. It is used to treat various ailments like diarrhea, flatulence, toothache, amenorrhea, leucorrhea, fever, headache, common cough and cold. For throat infection, the regular use of the cinnamon is capable of averting the contagions (Hajimonfarednejad *et al*., 2018).

Ojagh *et al*. (2012) reported that its bark holds 21 phytochemicals, among them cinnamaldehyde and eugenol are the two major components. Many studies have revealed that the bark extract has antioxidant, antimicrobial, antiviral, antidiabetic, antihypertensive, antitumor, gastroprotective, and immunemodulatory activities (Shen *et al*., 2012). It was reported that the elevated dose of it promotes both cell-mediated and humoral immunity, while the lower dose exhibited an effect on humoral immunity only, hence the bark of this plant can be used as immunity enhancers (Niphade *et al.*, 2009), Recently, Moshaverinia *et al*. (2020) considered the outcome of hydroalcoholic extract of cinnamon on the infectivity of herpes simplex virus-1 (HSV-1) and reported that the hydroalcoholic extract was efficient in dipping the viral titer of HSV-1 by avoidance of viral attachment to the host cells. This property of the cinnamon can be further investigated in relation to prevention of SARS-CoV-2.

2.3 *Glycyrrhiza glabra* L.

Glycyrrhiza glabra L. is a member of family Fabaceae; it is one of the most admired medicinal plants worldwide. It is also known as liquorice, licorice, sweet wood, glycyrrhiza, *etc*. This species is a inhabitant of Mediterranean region and frequently found in India, China and Russia.

The extracts of *G. glabra* have been used in food and pharmaceutical industries (Herrera *et al*., 2009). The medicinal uses of liquorice are also mentioned in traditional and folk remedies (Armanini *et al.*, 2002). The initial credentials can be obtained in ancient Egyptian, Assyrian, Indian and Chinese cultures. The ancient botanist, namely; Theophrastus and Dioscorides also wrote about the medicinal properties of liquorice and explained its curative uses (Armanini *et al*., 2002). In long-established medicinal systems, *G. glabra* is suggested as a regular medication for cough, bronchitis, gastrointestinal problems and arthritis. Generally, the roots of *G. glabra* are utilized to prepare a decoction that is an exceptional dehydration quencher and perfect medication in cases of throat infections.

The phytochemistry of *G. glabra* has been widely investigated (Hayashi *et al*., 2016). It was found that *G. glabra* is a good source of simple sugars and polysaccharides, starch, proteins, amino acids, mineral salts, resins, pectins, gums and sterols (Wang *et al*., 2015). Likewise tannins, oestrogens, coumarins, phytosterols, vitamins,

and glycosides have also been reported (Wang *et al*., 2015). Later, good quantities of bioactive compounds have been isolated, including saponins (responsible for the sweet taste), triterpenes, and flavonoids (Rizzato *et al*., 2017). The main constituent isolated was glycyrrhizin, which is a triterpenoid saponins and estimated 50 times sweeter compared to sucrose (Yu *et al*., 2015).

The flavonoids are responsible for the characteristic yellow colour of liquorice. The most important flavonoids reported are glycosides of liquiritigenin (42 ,7 dihydroxyflavanone) and isoliquiritigenin (22 ,4,42 trihydroxychalcone) (Rizzato *et al*., 2017). Moreover, several volatile phytoconstituents (hexanol, pentanol, geraniol, terpinen 4 ol, and α terpineol) are present in roots giving the typical odor. The essential oil extracted from *G. glabra* is also prosperous in propionic acid, furfuraldehyde, furfuryl formate, benzoic acid, 1 methyl 2 formylpyrrole, 2,3 butanediol, maltol, and trimethylpyrazine (Chouitah *et al*., 2011; Pastorino *et al*., 2018).

G. glabra is one of the oldest and most preferred herbal medicines worldwide. Many of the past uses of it in healthcare are well recognized. It has remarkable antioxidant, anti-inflammatory, antitussic, antiulcerative, antimicrobial, anticarcinogenic, antimutagenic, hepato-protective, neuro-protective, sedative, antidepressive and antiviral activities.

The antiviral activity of *G. glabra* extracts against a range of viruses was done, including *Varicella zoster*, Herpes simplex, influenza, Japanese encephalitis, and vesicular stomatitis virus. The studies have confirmed that two tri-terpenoids (glycyrrhizin and 18α glycyrrhetinic acid) are accountable for the antiviral activity. These two tri-terpenoids have the capacity to restrain gene expression and replication of virus and also able to decrease the adhesion strength along with the reduction in HMGB1 binding to DNA (Wang *et al*., 2015). Furthermore, they can augment host cell activities by jamming the deprivation of IλB enzyme concerned in the spread of the cellular reply to irritation, activating T lymphocyte proliferation, and holding back apoptosis of the host cell (Wang *et al*., 2015). The antiviral methods of both compounds are alike, slowing down the adsorption and penetration of the virus in the initial steps of the replication cycle.

The antiviral potential of glycyrrhizin against severe acute respiratory syndrome virus (SARS) was also evaluated and it was reported that glycyrrhizin influences the cellular signaling pathways for instance protein kinase C, casein kinase II, and transcription factors, specifically, activator protein 1 and nuclear factor κB which has potential to stop the propagation of virus (Cinatl *et al*., 2003).

2.4 *Piper nigrum* L.

Piper belongs to family Piperaceae and designated as the 'king of spices' due to its strong smell. *P. nigrum* is usually grown in tropical countries like India, Brazil and Indonesia. It has noteworthy biological characteristics and its bioactive compounds are utilized as preservative, medicine and perfumery. An alkaloid called piperine (1-peperoyl piperidine) is extracted from this plant and extensively used in the Ayurveda, Unani, Siddha and Tibetan systems of medicine. The alkaloid, piperine is known to hold numerous appealing pharmacological impending, *viz*., antioxidant, analgesic, antidepressant, antihypertensive, antiplatelets, anti-Alzheimer's, anti-inflammatory, antimicrobial, antipyretic, antiasthmatic, antitumor, *etc*. (Tiwari *et al*., 2020).

P. nigrum has been evaluated for its antiviral potential. The antiviral activity of it was estimated using its extracts in chloroform and methanolic extract in opposition to an enteric virus vesicular stomatitis virus (VSV) and human parainfluenza virus (HPV) on human cell lines and it was observed that the extract in chloroform performed better as antiviral agent than the methanolic extract due to the presence of higher content of alkaloids (Priya and Saravana, 2017). Later, the molecular docking studies revealed that piperine (1-peperoyl piperidine) is somewhat more capable to restrain VP35 interferon inhibitory domain of Ebola virus and methyltransferase of Dengue virus comparative to commercial antiviral Ribavirin (Nag and Chowdhury, 2020). Rajagopal *et al*. (2020) reported that the bioactive piperdardiine and piperanine from *P. nigrum* are noticeably active against COVID-19, and can be further validated for medication against this virus.

2.5 *Syzygium aromaticum* L.

Syzygium aromaticum L. (clove) belongs to the family Myrtaceae, and well known worldwide for its uses in medications as an antiseptic agent against communicable diseases owing to its antimicrobial potential. *S. aromaticum* is also used in the food industry to increase shelf-life of food products because of its antimicrobial nature. Clove has many bioactive compounds, *viz*., flavonoids, hydroxybenzoic acids, hydroxycinamic acids, and hydroxuphenylpropens. The main bioactive constituent of clove is eugenol (Neveu *et al*., 2010), which exhibits extensive antimicrobial efficacies against gram-positive, gram-negative, and acid-fact bacteria, and pathogenic fungi. Eugeniin, a phytochemical isolated from the extracts of *S. aromaticum* was reported as anti-Herpes Simplex virus agent. The inhibitory action of eugeniin influences the viral DNA synthesis by performing as a discriminating inhibitor of the HSV-1 DNA polymerase while the compound eugenol inhibits viral replication and reducing infection (Reichling *et al*., 2009).

2.6 *Zingiber officinale* Roscoe

Zingiber officinale Roscoe (ginger) belongs to family Zingiberaceae and is one of the most important plants in terms of medicinal uses. In conventional systems of medicine like Ayurveda and Unani, *Z. officinale* is one of the most used plants in their formulatiinse (Bashir and Afrin, 2019). It is is a rich source of bioactive phytochemicals, *viz*., phenols, alkaloids, steroids, *etc*. The principal aromatic compound is zingiberol which is extracted from its rhizome. In addition to this compound, it also contains some other bioactive phytoconstituents, *viz*., 4-gingerol, 6-gingerol, 8-gingerol, 10-gingerols, 6-shogaols, and 14-shogaols (Ali *et al*., 2008).

Owing to this phytochemistry, ginger demonstrates antipyretic, anti-inflammatory, antiemetic, analgesic and antiarthritic activities. Apart from these useful medicinal properties, the bioactive compounds of ginger showed efficient inhibitory action against many viruses which include Herpes simplex virus (HSV), Chikungunya virus, Influenza virus, Human respiratory syncytial virus and SARS-CoV-2 (Admas, 2020; Sulochana *et al*., 2020). For instance, Wahab *et al*. (2009) have reported the antiviral activity of lyophilized juice mined from ginger. They found that at varying concentration from 5-200 µg/ml, the extract was capable to inhibit the replication of hepatitis C virus and recommended the 100 µg/ml doses for effective control on the viral replication. Recently, Ahkam *et al*. (2020) done a molecular docking study to find out the prospective of gingerenone A, geraniol, gingerol,

shogaol, zingiberenol, zingiberene and zingerone regarding prevention of SARS-CoV2, they found that these bioactive compounds of ginger are effective as anti-SARSCoV-2 agents because they have the ability to interact with the spike and main protease (Mpro) protein. These bioactive compounds obstruct the spike (S) protein from binding to the ACE2 receptor or work as an inhibitor for MPro. In this way, these phytoconstituents not only obstruct the binding but also the viral replication inside the host (Walls *et al*., 2020).

3. Discussion

The SARS-CoV-2 is highly contagious disease against which apart from few vaccination programs, there is no effectual therapy available till date (Guan *et al*., 2020). However, if the immunity of people can be enhanced, then this ongoing fight can be won. The fight between these pathogens and humankind is not new and it is evident that humans always appeared as winner against such types of pandemic through their knowledge about the nature. In olden times when there were no allopathic medication and vaccination available, the sole source of survival was the plants. In ancient literatures several plants have been mentioned for their medicinal significance which include many spices and herbs; for example, tulsi, mulethi, adrak, pyaz, lehsun, haldi, dal cheeni, *etc*., and traditionally people took kadha (decoction) of these ingredients to treat many of the day-to-day diseases. In case of respiratory problems/infections, the use of kadha/ decoction which was prepared with clove, ginger, black pepper, cinnamon, and tulsi as main ingredients was recommended. In recent, time these plants/plant products are still the major ingredients of herbal formulations such as 'Coronil kit' a Patanjali product. This proves that these spices and herbs play important role in prevetion of SARSCoV-2 (COVID-19) and other viral infections.

During the last two years of pandemic, the value of these spices and herbs has been greatly enhanced as immunity boosters worldwide and according to ASSOCHAM, India (June-2020), the export of such spices showed 23% increase during COVID-19. The major nations where the spices are being traded include the United States, Australia, Germany, United Kingdom, Italy, France, Iran, Bangladesh, Canada, Singapore, UAE, China, *etc*., which shows that the humankind is benefitted by these miraculous herbs and spices.

4. Conclusion

In the existing pandemic situation, safety measures and enhancing immunity are most gettable options to avoid COVID-19 contagion. In this direction, the uses of certain spices and herbs can do miracle for humankind against SARS-CoV2. The antiviral potential of six commonly used plants in Ayurveda and Unani formulations, *viz*., *Cassia fistula*, *Cinnamomum* spp., *Glycyrrhiza glabra*, *Piper nigrum*, *Syzygium aromaticum*, and *Zingiber officinale* have been discussed as they are frequently used to enhance immunity against SARS-CoV-2. Since, these plants are present as main ingredients in many herbal formulations against respiratory problems and "Coronil kit' which was popularized as effective medication against SARS-CoV-2 (COVID-19). Based on the previous valid publications, it can be said that these plants have great potential and can play a vital role against SARS-CoV-2 (COVID-19) as they were found effective on other viral infections. Apart from this, the mentioned plants have other health benefits owing to that they are in use in many conventional medicinal systems. Now, more comprehensive studies about the bioactive compounds present in these commonly growing plants, their efficiency, doses and mode of action in opposition to fatal viruses need to be ascertained.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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